REMARKS

Claims 1-25 and 28-45 and 48-50 remain in this application. Claims 26-27 are cancelled. Claims 18, 19 and 21 have been withdrawn as the result of being drawn to a non-elected species, while claims 28-45 and 48-50 have been withdrawn as a result of an earlier restriction.

In view of the Examiner's earlier restriction, applicants retain the right to present the subject matter of withdrawn and cancelled claims in subsequent prosecution.

Applicants' prior response of June 23, 2005 was not considered in its entirety due to the loss of the Carpenter *et al.* reference during processing of the response. A duplicate copy of the reference was submitted in Applicants' After-Final Response dated November 4, 2005. In the Advisory Action mailed December 9, 2005, the Examiner did not find Applicants' arguments sufficiently persuasive and maintained all of the outstanding rejections presented in the Office Action of August 8, 2005.

Applicants hereby submit additional arguments, have canceled claims and request reconsideration and allowance.

The Rejection under 35 U.S.C. § 103(a) over Andya (WO 97/04801) in view of Relton *et al.* (WO 97/45140), Kaisheva *et al.*, (US2003/0113316) and Merck Index (Merck Index, 10th Ed., 1983, pp. 797-798).

The Examiner alleges that Andya discloses antibody formulations having an osmotic pressure of 250-350 Osm (p. 9, lines 6-9, Fig. 13), antibody concentrations ranging from at least 80 mg/ml to 300 mg/ml (p.3, lines 8-10), lyoprotectants (*e.g.*, sucrose, trehalose) ranging from 30 mM to 300 mM (p. 15, lines 8-15) and various administration methods including injection devices, including syringes and auto-injectors (p. 17, lines 30-35).

The Examiner has further asserted that the claimed invention only differs from Andya by the recitation of arginine-HCl in the formulation and having a kinematic viscosity less than 50 cs.

In response, Applicants note for the record that Andya *et al.* is directed to reconstituted lyophilized formulations, whereas the present invention is directed to stable liquid formulations. The distinction is important because stable liquid formulations pose different challenges. For example, whereas a difference in solvent volume between the pre- and post-lyophilization process can effectively increase the protein concentration (along with other dissolved solids), a stable liquid formulation must be prepared without the evaporation and reconstitution step.

One particular challenge posed by a stable liquid formulation is shelf life. Since a lyophilized formulation is typically reconstituted immediately prior to administration, excipients (*e.g.*, lyoprotectants) need not be selected for long term stability - the primary concern is with protecting the protein therapeutic during the freeze-thaw and reconstitution process. In fact, Andya *et al.* even recognizes long term stability after reconstitution is a problem (see Figures, Examples). Indeed, it is dry storage that is proposed by Andya *et al.* to solve this problem of storage stability (see page 1, lines 21-30 in particular). However, as described in Figure 9 of the present application, trehalose (one of the Andya excipients) is simply unsuitable for the present formulation because it does not provide sufficient long term stability.

Another significant challenge of high concentration formulations is viscosity. As the amount of dissolved solids in a solution increases, so increases viscosity. Certain excipients increase viscosity to a much greater extent than others. As Applicants have previously stated, at high protein concentrations, the complexity of problems in creating acceptable formulations is greatly multiplied. In the lyophilized formulations of Andya, the "cryoprotectants" sucrose and trehalose were mainly present in order to reduce the stresses caused by the freezing, thawing and drying processes. However, in the instance of the liquid formation of the present invention, the Andya *et al.* excipients (*e.g.*, trehalose, sucrose) either increase viscosity or do not decrease viscosity to an acceptable level (*i.e.*, 50 cs or less). In fact, the Examiner has indicated in the December 9, 2005 Advisory Action that lower viscosity is an expected property.

Applicants most certainly agree that a lower viscosity is desirable. However, how this may be achieved while balancing the other needed requirements of a formulation is precisely the

point. One of Applicants' key discoveries is that increasing ionic strength of the formulation also decreases viscosity. However, the amount of excipient that may be added to increase the ionic strength and thereby lower the viscosity is limited by the osmotic pressure limitation (essentially a measure of total dissolved solids). Thus, a careful selection of excipients is required, and that the excipients which are chosen must play multiple roles of stabilizers, buffers, tonicity modifiers, ionic strength enhancers, *etc.*

None of the above is appreciated or disclosed by Andya *et al.* Thus, it is simply the case that the excipients disclosed by Andya *et al.* are unsuitable for use in the formulations of the present invention.

The deficiencies of Andya *et al.* are not remedied by Kaisheva. Thus, while Kaisheva discloses that arginine may be suitable for use as a pharmaceutical excipient, it does not teach how to create a high concentration protein formulation (*e.g.*, 100 to 260 mg/ml) in a manner which balances stability, buffers, tonicity and ionic strength. These deficiencies are further not remedies by either of the remaining references, Relton *et al.*, or Merck Index.

SUMMARY

Claims 1-25 and 28-45 and 48-50 are pending in the application.

If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and no fees are believed due for timely consideration. In the unlikely event that fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: **January 6, 2005**

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